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# Increased adrenal epinephrine and norepinephrine in spontaneously hypertensive rats treated with hyperbaric oxygen

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# INCREASED ADRENAL EPINEPHRINE AND NOREPINEPHRINE IN SPONTANEOUSLY HYPERTENSIVE RATS TREATED WITH HYPERBARIC OXYGEN

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Adrenal catecholamines were determined in Wistar Kyoto rats (WKY), and stroke-prone and stroke-resistant spontaneously hypertensive rats (SHRSP, SHR) treated with hyperbaric oxygen for 90 minutes daily from 6 to 13 weeks of age. The animals were divided into 5 groups. Group I (control group), was handled under the same conditions as pressure-treated groups II and III, but with ambient oxygen pressure and concentration. Group II (pressure-control group), was treated with 2 atmospheric absolute pressures (ATA) of air without any oxygen provided. Group III (high-oxygen group), was exposed to 2 ATA under the environment of air saturating oxygen. Group IV (antihypertensive group), was treated with hydralazine. Group V (adrenalectomized group), was given 1% NaCl solution and bilateral adrenalectomy.

The average contents of adrenal norepinephrine of SHR and of SHRSP in Group I were greater ( $p < 0.05$ - $p < 0.001$ ) than those of the WKY in Group I. A similar tendency was also observed for the content of adrenal epinephrine. The average concentrations of adrenal epinephrine and norepinephrine of SHR and SHRSP in Group II and III were significantly ( $p < 0.05$ - $p < 0.001$ ) greater than those of the respective rats in Group I, but no significant differences were noted in the blood pressure between pressure-treated groups (II, III) and the control group (I). Adrenalectomized SHR, SHRSP and WKY rats (Group V) had similar blood pressure levels as the control rats (Group I). The development of hypertension in SHR and SHRSP was effectively suppressed by the treatment with hydralazine, which, however failed to reduce concentrations of adrenal epinephrine and norepinephrine in these rats.

These results indicate that increased adrenomedullary function in SHR and SHRSP is further enhanced by hyperbaric oxygenation treatment, but that high concentrations of adrenal catecholamines are not required for the pathogenesis of spontaneous hypertension of these animals at this age.

**Key words:** High-performance liquid chromatography, Adrenal catecholamine, SHR, Hyperbaric oxygenation, Hydralazine

## INTRODUCTION

Hypertensive vasocontractility which leads to an increased discharge of the sympathetic nervous system or high level

of catecholaminergic humoral substances has been reported to elevate blood pressure in genetically hypertensive rats<sup>8,10,17)</sup>

Inhalation of pure oxygen at 3 ATA produced an oxygen tension 15 to 20 times

higher than normal in human arterial blood<sup>14)</sup>. In addition, exposure to 2 ATA alone or together with oxygen saturation for 90 minutes daily for 26 successive days has been shown to result in increased adrenocortical function in rats and human beings<sup>15)</sup>. However, few endocrinological studies dealing with the adrenal medulla of the genetically hypertensive rat under the influence of hyperbaric oxygenation have been made. We investigated whether intermittent exposures to hyperbaric oxygen might alter the concentrations of adrenal catecholamines in stroke-prone and stroke-resistant spontaneously hypertensive rats whose genetically inherited hypertension might be attributed to the discrete abnormality of the adrenal gland.

#### MATERIALS AND METHODS

Age-matched male Wistar Kyoto rats (WKY), spontaneously hypertensive rats (SHR) and stroke-prone spontaneously hypertensive rats (SHRSP) were obtained and kept under the same conditions throughout the experiment unless otherwise stated. They were fed rat chow (Japan Clea Co., CE-II) (0.28% sodium content) and distilled tap water *ad libitum*, and kept on a 12-hour light/dark cycle at 20°–22°C. For acclimation all animals were put in a hyperbaric chamber not containing oxygen saturated or compressed air from the 4th to 6th week of age. Then they were randomly divided into 5 groups and were treated as follows. Group I (control group), consisting of 10 WKY, 9 SHR and 7 SHRSP, was handled under the same chamber conditions as the pressure-treated Groups II and III, but with normal oxygen pressure and concentration. Group II (pressure-control group), consisting of 10 WKY, 10 SHR and 12 SHRSP, was treated with 2 ATA compressed air without providing oxygen. Group III (high-oxygen pressure group), consisting of 12 WKY, 12 SHR and 10 SHRSP, was exposed to 2 ATA in an environment of air saturated with 30 to 35% of oxygen for details on the hyperbaric oxygenation treatment see a

previous publication<sup>11)</sup>. Group IV (antihypertensive group), consisting of 9 SHR and 8 SHRSP was given hydralazine 100 mg/L in drinking water *ad libitum*. Group V (adrenalectomized group), consisting of 10 WKY, 11 SHR and 10 SHRSP, was given 1% NaCl solution to drink *ad libitum* and had bilateral adrenals removed. Systolic blood pressure of each conscious rat was measured once a week using the tail-pulse pick up method and an automatic blood pressure recorder model USM-105 (Ueda Instrument Co., Tokyo, Japan). At the end of this experiment, all animals were decapitated from 08.00–09.00 to avoid the circadian fluctuations in adrenal catecholamine concentration<sup>3)</sup>. Then adrenal glands were immediately removed, weighed, frozen on dry ice and preserved at –80°C. Catecholamines in tissues were purified and extracted with alumina based on the method of Maruyama *et al.*<sup>6)</sup> or Hjemsdahl *et al.*<sup>4)</sup> after slightly modification. Each pair of adrenal glands was homogenized in the mixture of 4.5 ml of 0.4 N HClO<sub>4</sub> and 0.5 ml of 0.01% cysteine under a chilled condition. The homogenate was subsequently centrifuged for 20 minutes at 10,000 × *g* at 4°C. Five  $\mu$ l of the supernatant was mixed with 200  $\mu$ l of 3,4-dihydroxybenzylamine (DHBA) (50 pg/ $\mu$ l), 1 ml of 0.05 M Tris HCl buffer at pH 8.5 and 50 mg of aluminum oxide. The combined mixture was slowly stirred for 20 minutes to absorb the catecholamines onto the aluminum oxide. The supernatant was discarded and the aluminum oxide was washed twice with 2 ml of distilled water. Then, this material was transferred to a conical centrifuge tube with a 0.2  $\mu$ m pore membrane filter (RC 58, Bioanalytical Systems Inc., U.S.A.) and centrifuged for 15 minutes at 2,000 × *G*. After the aluminum oxide was dried, 200  $\mu$ l of 0.1 N HClO<sub>4</sub> was added, and the eluted catecholamines were obtained after 15 minutes of centrifugation at 2,000 × *G*. After performing the final procedure for desorption of catecholamines, 25–50  $\mu$ l of standard solution containing approximately 2 p moles of the catecholamines and DHBA or a similar volume of sample preparation extracted adrenal tissues was injected into

Table 1. Weight changes in total body and a pair of adrenal glands in rats treated with hyperbaric oxygen, hydralazine and adrenalectomy

Treatment	Rat strain	Body weight (g)		A pair of adrenal weights	
		Initial	Final	Wet weight (mg)	Body weight ratio (mg/100 g body weight)
Group I (control group)	WKY (10)	116 ± 4	230 ± 3	38 ± 3	16 ± 1
	SHR (9)	118 ± 3	228 ± 6	41 ± 2	18 ± 1
	SHRSP (7)	112 ± 3	224 ± 9	49 ± 4	20 ± 2
Group II (pressure-control group)	WKY (10)	120 ± 5	239 ± 6	41 ± 4	19 ± 1*
	SHR (10)	116 ± 2	229 ± 5	48 ± 4	22 ± 3
	SHRSP (12)	118 ± 4	226 ± 5	50 ± 3	24 ± 3
Group III (high-oxygen pressure group)	WKY (12)	124 ± 6	234 ± 4	45 ± 3	21 ± 2*
	SHR (12)	116 ± 5	230 ± 2	52 ± 3**	23 ± 2*
	SHRSP (10)	118 ± 2	220 ± 6	63 ± 4*	27 ± 2*
Group IV (antihypertensive group)	SHR (9)	120 ± 4	231 ± 5	39 ± 4	18 ± 2
	SHRSP (8)	114 ± 5	229 ± 6	51 ± 5	25 ± 4
Group V (adrenalectomized group)	WKY (10)	119 ± 4	232 ± 5		
	SHR (11)	116 ± 5	228 ± 6		
	SHRSP (10)	114 ± 5	222 ± 7		

Each value represents mean ± S.E.M. The numbers in parentheses represent the number of animals.

Significance of differences from Group I rats in the same strain: \* $p < 0.05$ , \*\* $p < 0.01$ Significance of differences compared to paired comparisons: + $p < 0.05$ , ++ $p < 0.01$

the high-performance liquid chromatogram (HPLC) system (LC-304 Bioanalytical Systems Inc., U.S.A.) and catecholamines were separated by chromatography on the column [pre-packed Perkin-Elmer ODS-Sil-X-1,  $250 \times 2.6$  I.D. (ODS)]. The mobile phase consisting of 28.3 g of monochloroacetic acid, 9.45 g of NaOH, 1.5 g of  $\text{Na}_2\text{EDTA}$ , 10 mg of sodium octyl sulfate and 2,000 ml of distilled water adjusted at pH 3.0 was percolated through 0.45  $\mu$  acetate filter and aspirated to remove gas bubbles in the solution. The aqueous solution of each sample injected into the chromatogram was analyzed in a RYT Recorder and LC-4A Amperometric Detector (Bioanalytical Systems Inc., U.S.A.) at flow rate of approximately 2 ml/min. The concentrations of epinephrine and norepinephrine were determined from their respective peaks using DHBA as the internal standard. The values for catecholamines determined as mg/g and  $\mu\text{g}$ /pair of adrenals will be referred to as (A) and (B), respectively. To determine statistical significance, the values were subjected to the Student's *t*-test.

### RESULTS

Exposures to 2 ATA with or without oxygen saturation for 90 minutes daily from the 6th to 13th week of age did not produce any abnormal activity state in the rats. All animals continued to gain weight during the experiment (Table 1). There was considerable variation in adrenal weight in each group (Table 1). High-pressure oxygen treatment increased the body weight ratio of adrenal glands in WKY, SHR and SHRSP ( $p < 0.05$ ), and also increased the wet weight of both adrenal glands in SHR ( $p < 0.01$ ) and SHRSP ( $p < 0.05$ ). The average body weight ratio of adrenal glands in rats treated with 2 ATA of air without providing oxygen (Group II) tended to be heavier than that of control rats (Group I), but this difference was not statistically significant except in WKY rats. The adrenal weight of SHRSP rats treated with hyperbaric oxygen (Group III) was 40% heavier ( $p < 0.001$ ) than that of WKY receiving the same

highoxygen pressure treatment (Group III). Fig. 1 illustrates the change in systolic blood pressures during the experiment. The blood pressures of control WKY (Group I) increased with time, reaching an average of  $124 \pm 2$  mm Hg (mean  $\pm$  S.E.) at the 13th week of age, whereas those of genetically hypertensive control rats (Group I) elevated markedly with time, the average being  $182 \pm 3$  mm Hg (mean  $\pm$  S.E.) in SHR and  $205 \pm 11$  mm Hg (mean  $\pm$  S.E.) in SHRSP at 13 weeks of age. The development of hypertension in SHR was relatively well suppressed by the treatment with hydralazine. The blood pressure of SHR which received hydralazine from the 6th to 13th week of age (Group IV) was 17% lower than that of the age-matched control SHR (Group I). Exposure of WKY, SHR and SHRSP to 2 ATA of air with or without oxygen saturation caused no discernible effect on blood pressure in these rat strains. The level of blood pressure of adrenalectomized SHRSP, SHR and WKY rats (Group V) was similar to that of the control rats (Group I). The chromatogram of the endogenous catecholamines from rat adrenal glands was compared with that of the mixture of standard catecholamines (Fig. 2). The mean recovery throughout the whole assay procedure was approximately 68%. Fig. 3 shows the adrenal epinephrine content. The adrenal epinephrine concentration of pressure-control SHR (Group II) was 22.9% (A) ( $p < 0.01$ ) or 49.5% (B) ( $p < 0.01$ ) greater than the control SHR (Group I). The adrenal epinephrine concentration of SHR treated with high-oxygen pressure (Group III) was 39.5% (A) or 48.7% (B) greater than that of the control SHR (Group I) ( $p < 0.001$ ). There was no discernible effect of hydralazine-treatment on the adrenal epinephrine concentration, and no significant difference in average epinephrine concentration was noted between control SHR (Group I) and antihypertensive-treated SHR (Group IV). The adrenal epinephrine concentration of pressure-control SHRSP (Group II) was 42.7% (A) or 26.1% (B) greater than of each control SHRSP (Group I) ( $p < 0.05$ , respectively). The adrenal epinephrine

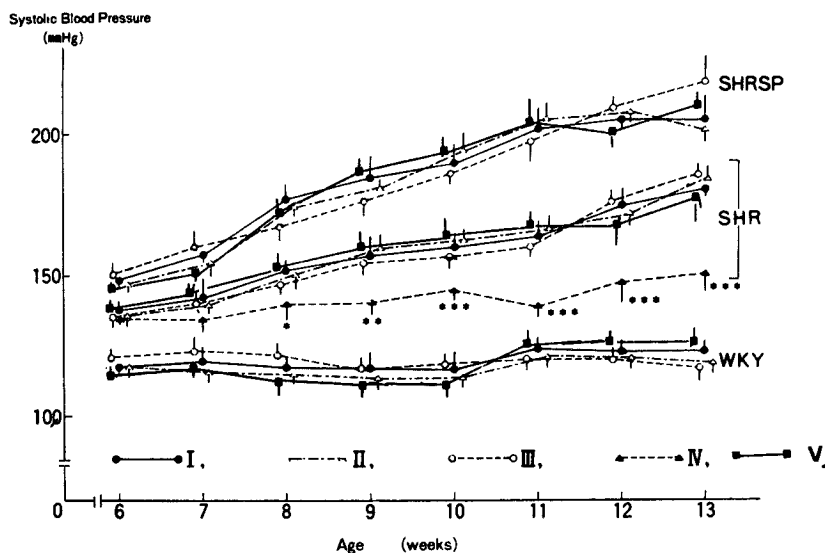


Fig. 1. Effects of hyperbaric oxygenation, antihypertensive therapy and adrenalectomy on blood pressures in WKY, SHR and SHRSP. Groups I to V each consisting of 17~34 rats were given the following treatments: Group I, control; Group II, pressure-control; Group III, high-oxygen pressure; Group IV, hydralazine; Group V, bilateral adrenalectomies. All animals were sacrificed at the age of 13 weeks as described in detail in MATERIALS AND METHODS.

Each bar represents the standard error of mean. Significance of differences from Group I rats (control) of the same rat strain: \* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.001$ .

concentration of SHRSP treated with high-oxygen pressure (Group III) was 55.9% (A) ( $p < 0.05$ ) or 41.2% (B) ( $p < 0.001$ ) greater than that of the control SHRSP (Group I). The adrenal epinephrine concentration of control SHR (Group I) and that of high-oxygen pressure-treated SHR (Group III) was 29.7% ( $p < 0.01$ ) and 65.4% ( $p < 0.05$ ) (B values) greater than that of the WKY, but the A values did not differ significantly. The adrenal epinephrine concentration of control SHRSP (Group I) was 68.4% (A) ( $p < 0.05$ ) or 137.5% (B) ( $p < 0.001$ ) greater than that of control WKY (Group I). The adrenal epinephrine concentration of high-oxygen treated SHRSP (Group III) was 111.3% (A) or 153.5% (B) greater than that of the similarly treated WKY (Group III) ( $p < 0.001$ , respectively). Fig. 4 shows the average concentration of adrenal norepinephrine. The norepinephrine concentration of pressure-control SHR (Group II) was

32.8% (A) ( $p < 0.05$ ) or 49.5% (B) ( $p < 0.01$ ) greater than that of respective control SHR. Hydralazine treatment did not alter the adrenal norepinephrine concentration in SHR. The adrenal norepinephrine concentration of pressure-control SHRSP (Group II) was 41.3% (A) ( $p < 0.01$ ) or 34.6% (B) ( $p < 0.05$ ) greater than that of the control SHRSP (Group I). The adrenal norepinephrine concentration of SHRSP treated with high-oxygen pressure (Group III) was 73.9% (A) ( $p < 0.05$ ) or 39.2% (B) ( $p < 0.01$ ) greater than that of the control SHRSP (Group I). The adrenal norepinephrine concentration of control SHR (Group I) was 57.8% (A) or 80% (B) greater than that of control WKY (Group I) ( $p < 0.001$ ). The adrenal norepinephrine concentration of high-oxygen pressure-treated SHR (Group III) was 70.7% (A) ( $p < 0.001$ ) or 76.1% (B) ( $p < 0.01$ ) greater than that of the similarly treated WKY (Group III). The adrenal norepinephrine

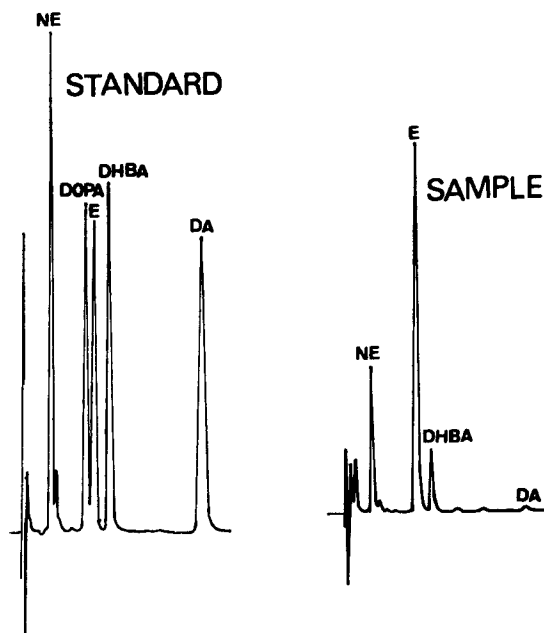


Fig. 2. The chromatogram of standard catecholamine mixture and that of a sample of adrenal extract using DHBA as an internal standard. NE ; norepinephrine, DOPA ; dopa (3,4-dihydroxyphenylamine), E ; epinephrine, DHBA ; 3,4-dihydroxybenzylamine, DA ; dopamine.

concentration of control SHRSP (Group I) was 38.6% (A) ( $p < 0.05$ ) or 116.7% (B) ( $p < 0.01$ ) greater than that of control WKY (Group I). The adrenal norepinephrine concentration of high-oxygen pressure-treated SHRSP (Group III) was 113.3% (A) or 113.9% (B) greater than that of the similarly treated WKY (Group III) ( $p < 0.001$ , respectively).

### DISCUSSION

The results of this investigation show that 2 ATA of air alone or together with oxygen saturation, for 90 minutes daily for successive 7 weeks, results in a significant increase of adrenal epinephrine and norepinephrine in stroke-prone and stroke-resistant spontaneously hypertensive rats. However, similar pressure treatment failed to increase adrenal catecholamines in WKY. The less pronounced response of adrenal catecholamines in WKY to the hyperbaric oxygenation treatment might be the result

of genetic determinants.

A critical relationship is known to exist between the time of exposure and the partial pressure of oxygen<sup>53</sup>. Hyperbaric oxygenation has no beneficial effect unless sufficient time is allowed and pressure can be well tolerated by the host or animal<sup>133</sup>. The experimental conditions designed in this study appear to be suitable since this hyperbaric oxygenation treatment could well stimulate adrenocortical function in genetically hypertensive rats. Evidence has been presented that the release of norepinephrine in response to nerve stimulation is increased in SHR compared to WKY<sup>23</sup>, and that the development of hypertension and increased non-collagenous protein synthesis of small arteries in young SHR can be concomitantly prevented by splanchicotomy and treatment with hexamethonium or clonidine, but the increased non-collagenous protein synthesis cannot be suppressed by a vasodilator (hydralazine)<sup>12,17</sup>. These findings indicate that the

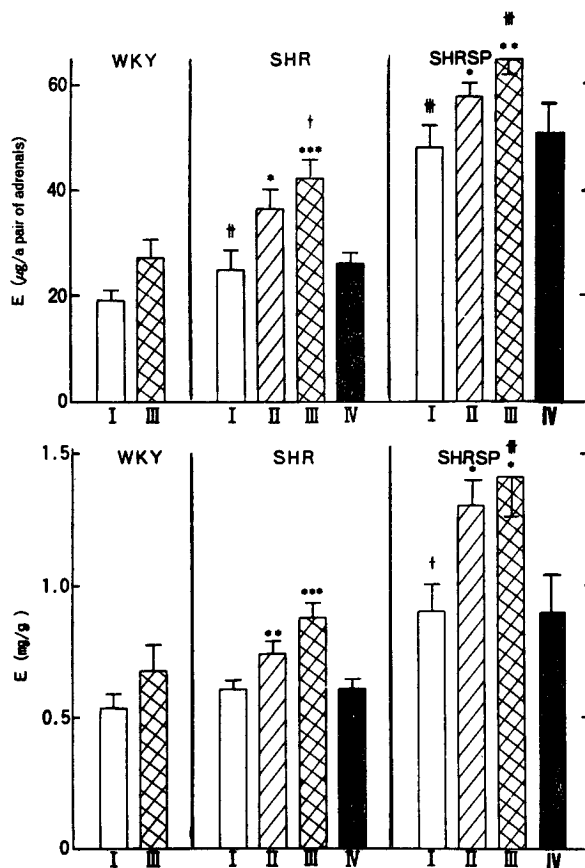


Fig. 3. Concentration of adrenal epinephrine (E) of rats at the age of 13 weeks. Groups I to IV (abscissa) were same as those in Fig. 1. Columns with vertical bars represent mean  $\pm$  S.E.M. Significance of differences from Group I rats (control) of the same strain: \* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.001$ . Significance of differences from WKY in the same treatment: + $p < 0.05$ , ++ $p < 0.01$ , +++ $p < 0.001$ .

sympathetic nervous system contributes to the development of hypertension in SHR. In our study, increased concentrations of adrenal epinephrine and norepinephrine in SHR and SHRSP were not altered by the treatment with hydralazine, which however, decreased the blood pressure during the experimental period. The exact sequence of events have to be identified. Since increased content of catecholamine can be attributed to the possibility of increased catecholamine synthesis without changing its secretion, decreased catecholamine secretion without changing its synthesis or a combination of both phenomena. Because of the difficulty in analysing the turnover of

catecholamines, only the catecholamine content was determined in this study. However, the level of blood pressure of the control group (Group I), was similar to that of the pressure control group (Group II), high-oxygen pressure-treated group (Group III) and adrenalectomized group (Group V) from the 6th to 13th week of age in SHR and SHRSP. These results suggest that increased epinephrine and norepinephrine in SHR and SHRSP at 13 weeks of age is not the only factor related to the pathogenesis of hypertension. According to Nagatsu et al.<sup>9)</sup>, both DBH and tyrosine hydroxylase activities in the adrenal glands were significantly greater in SHR than in WKY



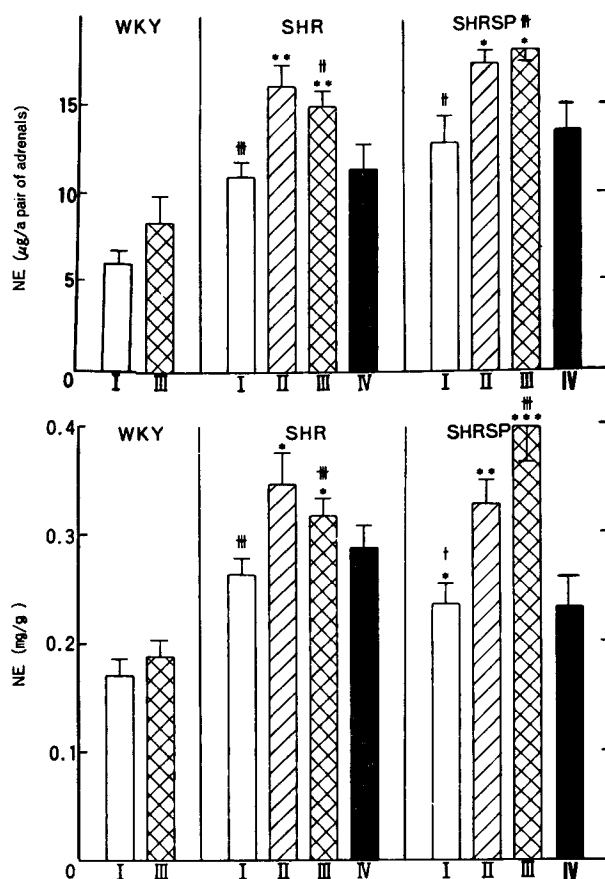


Fig. 4. Concentration of adrenal norepinephrine (NE) of rats at the age of 13 weeks. Groups I to IV (abscissa) were same as those in Fig. 1. Schematic representations as in Fig. 3. Significance of differences from Group I rats (control) of the same strain: \* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.001$ . Significance of differences from WKY in the same treatment: + $p < 0.05$ , +++ $p < 0.001$ .

at 16 weeks of age, but both enzymatic activities in both SHR and WKY were similar at 3 weeks of age. The difference in DBH activity between WKY and SHR might be due to genetic derivation or might be attributed to the compensatory reduction of the sympathetic nerve activity in genetically hypertensive rats after the establishment of hypertension. Special attention must be paid to the adrenal weight. The wet weight of SHRSP is 28.8% ( $p < 0.05$ ) and 40% ( $p < 0.01$ ) greater than that of control WKY in Group I and Group III, respectively (Table 1). Hypophysectomy

resulted in significant reduction in activities of adrenal tyrosine hydroxylase, DBH and phenylethanolamine-N-methyltransferase in the rat, and these enzymatic activities can be restored to near normal levels by ACTH administration<sup>7,16</sup>. In addition, compensatory adrenal hypertrophy following unilateral adrenalectomy was accompanied by a significant increase in adrenal DBH activity<sup>17</sup>. Although, corticosteroids and ACTH were not measured in the present experiment, 2 ATA alone or together with oxygen saturation for 90 minutes daily for 26 successive days has been shown

to result in a significant increase of plasma corticosterone concentration<sup>15)</sup>. In conclusion, the present experiment has clarified two important points. First, hyperbaric oxygenation treatment induces an increase in the level of adrenal epinephrine and norepinephrine in SHR and SHRSP. Second, it also raises the body weight ratio of adrenal glands in normotensive and genetically hypertensive rats. Although it remains unclear whether these changes are caused by increased levels of corticosteroid or ACTH, pituitary-adrenocortical axis appears to be important for the regulation of adrenomedullary catecholamine biosynthetic enzymes or their metabolites. The morphological and physiological basis for adrenal mediation of catecholamine abnormality must be pursued in future.

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## 和文抄録

高圧酸素の副腎エピネフリン・ノルエピネフリン含量増加作用  
—とくに高血圧自然発症ラットを中心として—

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家 森 幸 男

ウィスター京都ラット (WKY), 高血圧自然発症ラット (SHR), 高血圧自然発症脳卒中易発症ラット (SHRSP) を5群に分け, 6週齢より13週齢まで以下のごとき実験操作を連日施行した. 第Ⅰ群は対照群, 第Ⅱ群は大気下における絶対圧2気圧の高圧酸素処置群, 第Ⅲ群は高濃度酸素環境下における高圧酸素処置群, 第Ⅳ群は hydralazine 投与群, 第Ⅴ群は1%飲料食塩水投与下における副腎剔除群である.

第Ⅰ群の SHR, SHRSP の副腎中のエピネフリン (E), ノルエピネフリン (NE) 含量は同群の WKY のそれより高値であった ( $p<0.05$ — $p<0.001$ ). 同様の傾向が副腎E含量についても認められた. 第Ⅱ, Ⅲ群の SHR, SHRSP の副腎 E・NE 含量は第Ⅰ群

の SHR, SHRSP のそれよりそれぞれ高値を示した ( $p<0.05$ — $p<0.001$ ). しかし両群間の strain-matched hypertensive rats の血圧は同レベルであった. 副腎剔除術 (V) はどの rat strain にも有意の血圧変動を惹起させなかった. hydralazine (Ⅳ) 投与は SHR, SHRSP の血圧を低下させたが, 副腎 E・NE 含量に有意の影響を与えなかった.

以上の成績より, SHR, SHRSP の副腎髄質機能が高圧酸素処置により亢進することが証明された. また同時に, 副腎髄質機能の亢進がこれらの動物の高血圧の pathogenesis とほとんど無関係であることが判明した.